Original Article

Efficacy and tolerability of perampanel in pediatric patients with Dravet syndrome

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Background: In 1978, Charlotte Dravet first described a form of epilepsy termed Dravet syndrome (DS). It is a form of genetic epilepsy with early-onset, intractable epilepsy episodes, and neurodevelopmental delay. In children, DS can lead to refractory seizures that are resistant to standard therapy. Recently, perampanel (PER) was approved as an antiepileptic drug for patients as young as 4 years old.

Methods: The medical records were retrospectively reviewed and patients with DS who used PER were included in this study. The diagnosis was established using whole-exome sequencing, and the collected data included the patients' demographic characteristics, seizure pattern, PER dosage, laboratory and imaging findings.

Results: This study included 18 pediatric patients with a clinical diagnosis of DS. The mean age of PER initiation was 7.67±3.865. Most patients had two types of seizures (61.1%) followed by three types (22.2%), with generalized tonic-clonic being the most frequently reported type of seizure. The mean efficacy of PER was 29.17%±29.368%, and only one patient had an efficacy of 100%. Moreover, patients aged 8 years and younger presented with higher efficacy than those who were older (49.17%±34.120% *vs.* 19.17%±21.829%, P=0.03).

Conclusions: This study presented supporting evidence of the promising therapeutic effect of PER among patients with DS. PER can be considered one of the treatment options for this group of patients. However, several patients presented with unfavorable side effects that led to medication cessation. Future multicenter studies are required to explore further treatment options for patients with DS.

Keywords: Dravet syndrome (DS); generalized tonic-clonic seizure (GTCS); perampanel (PER); epilepsy; anti-seizure drug

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Introduction

Epilepsy is a chronic brain disorder characterized by the tendency to develop recurrent unprovoked seizures at least 24 hours apart. In 2017, the International League Against Epilepsy (ILAE) established a classification of seizures and epilepsies (1), which aided clinicians in different diagnostic and therapeutic approaches depending on the form of epilepsy. In 1978, Charlotte Dravet first described a form of seizure termed Dravet syndrome (DS), previously known as severe myoclonic epilepsy of infancy (SMEI) (2). It is a form of genetic epilepsy with early-onset and rare prevalence. It manifests as intractable epilepsy with multiple seizure patterns and neurodevelopmental delays (3). Remarkably, the vast majority of patients with DS carry a *de novo* mutation in the *SCN1A* gene (4,5). This gene encodes for the alpha-one subunit of the voltage-gated sodium channel (6). The sequence variants in the mutated gene result in a broad spectrum of clinical features ranging from asymptomatic carriers to severe epilepsy phenotypes (7). Additionally, 20–30% of phenotypical DS patients could have other mutations (8,9). In the pediatric population, DS can lead to refractory seizures that are resistant to therapy and occasionally present in severe forms that are associated with regression of the normal development in the child's first few years of life (especially during the first 4 to 6 years). Other features like cognitive decline, intellectual disability like hyperactivity and attention deficit, and oppositional defiant behavior could also be present in pediatric patients with DS (10). In 1990, DS was reported to have an incidence of 1:40,000 live births (11). However, in another study conducted in 1992, the figures were reported to be between 1:20,000 and 1:30,000, with a male-to-female ratio of 2:1 (12). Many individuals with DS fail multiple anti-seizure medications (ASMs). As such, some studies investigated the role of ketogenic diet and presented data of its potential safe application, however, these studies were weakened with the level of evidence (13) and prominent compliance issues (14). As for the use of ASMs, a recent meta-analysis that assessed eight placebo-controlled trials on the efficacy of stiripentol, pharmaceutical-grade cannabidiol, fenfluramine hydrochloride, and soticlestat for patients with DS, the study presented first-class evidence that their use may support in the treatment paradigm to control seizure among patients with DS (15). The study proposed a superiority for fenfluramine hydrochloride and stiripentol in comparison to the other options, however, a higher risk of adverse events was reported among some of these medications which promotes the investigation of other pharmacological options that could potentially present with lower risks of adverse events and higher efficacy, especially given that such study limited with low number of evidence with some results being based on a single observation. Therefore, we discuss a new option, that is, perampanel (PER) which is a selective, noncompetitive antagonist of the αamino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptor (16) (*Figure 1*). PER was recently approved as an ASM for patients as young as 4 years old after it was indicated as an adjunctive treatment for partial-onset seizures in patients older than 12 years old and as an adjunctive treatment for primary generalized tonic-clonic seizure (GTCS) in patients with epilepsy at the same age group (17,18) and has been favored over other ASMs due to the ease of use of the titration scheme (19). Furthermore, PER showed efficacy and appropriate tolerability among other epilepsy syndromes that are known to be refractory to many ASMs including Lennox-Gastaut syndrome (20), nonetheless, firm conclusions are still not established on its use as a first-line treatment and more studies are needed to assess its long-term effects. It also presented potential in treating patients with refractory seizures compared to other ASMs (16), however, several possible adverse events for its administration have been reported such as dizziness, somnolence, headache, and fatigue which was frequently reported (21-23) as well as other psychiatric side effects (17,19,24). Moreover, only a few studies investigated and assessed the use of PER in patients with DS (24-30). In addition, studies conducted had a limited number of

Highlight box

Key findings

- We provided evidence of promising therapeutic potentials for perampanel (PER) among some patients with Dravet syndrome (DS), with clinical data supporting the value of this treatment.

What is known and what is new?

- PER was recently approved as an adjunctive anti-epileptic medication for patients as young as 4 years old for primary generalized tonic-clonic seizures.
- Patients who received the medication at the age of 8 years and younger had a significantly higher efficacy rate in comparison to older patients.

What is the implication, and what should change now?

- PER should be included in the treatment modality of patients presenting with epilepsy and genetically diagnosed with DS.

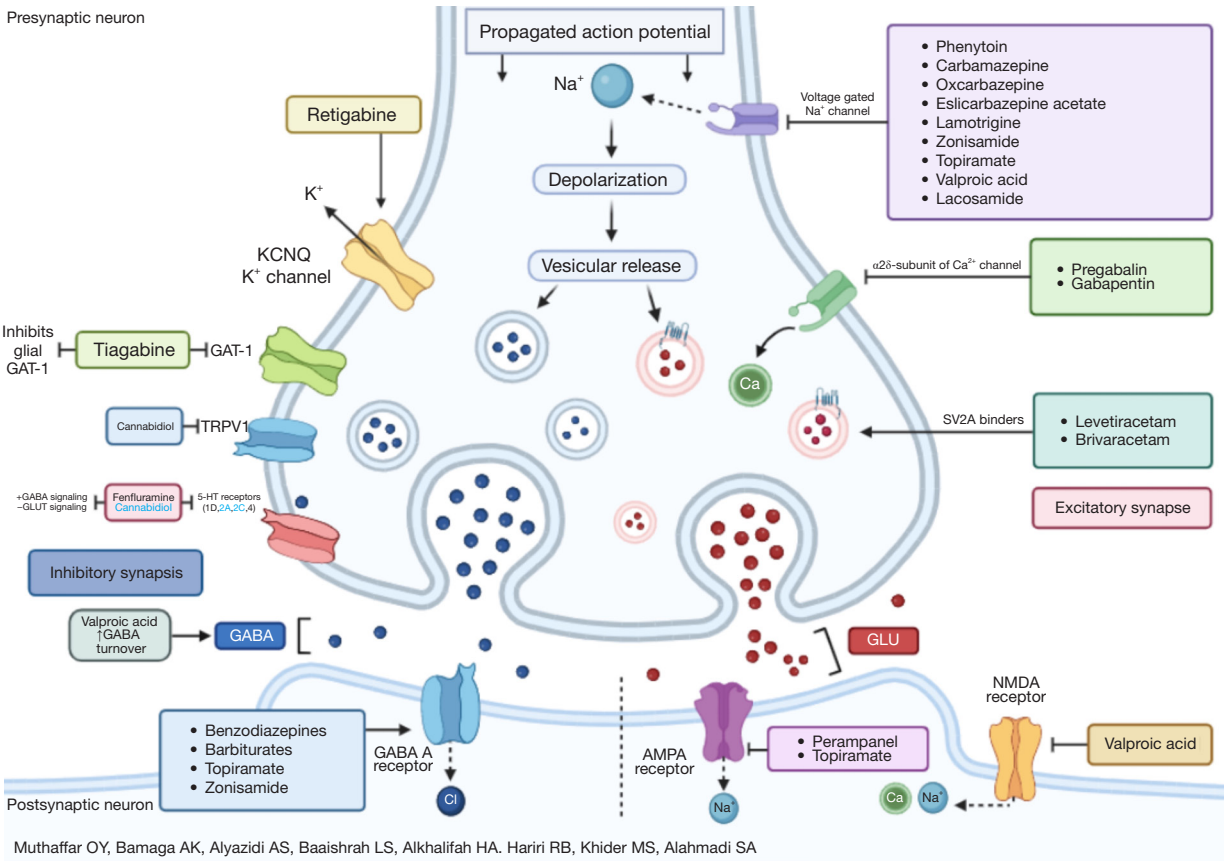

Figure 1 The spectrum of mechanism of action of main ASMs with effects on the inhibitory (left-hand side) and excitatory (right-hand side) nerve terminals. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; GABA, γ-aminobutyric acid; GLUT, glucose transporter; GAT-1, sodium- and chloride-depended GABA transporter 1; SV2A, synaptic vesicle glycoprotein 2A, GLU, glutamate; NMDA, N-methyl-d-aspartate; 5-HT, 5-hydroxytryptamine receptors; TRPV1, transient receptor potential vanilloid 1; ASMs, anti-seizure medications.

cases. Therefore, our study aims to assess the efficacy and tolerability of PER among pediatric patients with DS. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-581/rc).

Methods

Study design and setting

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Unit of Biomedical Ethics at the Faculty of Medicine at King Abdulaziz University approved this study (reference number: 244-23) on May 2, 2023. Informed consent was obtained from the parents or legal guardians of all patients. Informed consent was also obtained for off-label use of PER on the patients. Following the approval, we retrospectively reviewed the medical records of all pediatric patients (14 years and younger during the first admission) diagnosed with DS. The study extracted and included the data of all patients with a history of using PER or are currently on the medication. The search time frame was set from the date of PER approval that is October 2012 to August 2023. Patient records that did not indicate any PER prescription throughout their life were excluded. The diagnosis of DS was based on the following criteria: (I) refractory epilepsy with multiple seizure types including prolonged febrile convulsions, myoclonic jerks, atypical absences, GTCS and complex focal seizures; (II) seizure before 1 year of age in a previously normal infant; (III) developmental delay; (IV) electroencephalogram (EEG) with generalized spike and polyspike waves; (V) genetic diagnosis of *SCN1A* mutation or other reported genetic variants that

can present with DS like: *PCDH19*, *SCN1B*, *GABRA1*, *STXBP1*, *CHD2* and *SCN2A*. The criteria were based on the ILAE 2022 definition. We evaluated seizure frequency before and after administering PER and the adverse events that occurred following its administration. Patients were followed for at least 3 months to determine the efficacy of PER. PER treatment was considered effective when seizure frequency had been reduced by more than 50%. We continued observation until the dose of concomitant ASMs had increased or until patients started taking another ASM. Adverse events were determined via physical examination, laboratory testing, or based on reports from patients and their families. The collected data included age, gender, seizure onset, seizure type and semiology, genetic mutations, age of PER initiation, duration of PER usage, PER maximum dose, the number of concomitant ASMs, past failed ASMs, PER efficacy, EEG, and magnetic resonance imaging findings.

Statistical analysis

Data were entered into Microsoft Excel version 20. A descriptive statistical analysis was conducted using the Statistical Package for the Social Science (SPSS) version 25 (IBM© Corp., Armonk, NY, USA). Measures of central tendency were calculated to describe quantitative variables, while frequencies and percentages were used for categorical variables. Person correlation was used to assess the relationship between the age and the dose with the drug efficacy. While independent *t*-test was used to assess the relationship between the age groups (≤8 and >8 years) with the drug efficacy. The drug retention probability curves were calculated by the Kaplan-Meier method. Confidence interval was set at 95% and P value were considered statistically significant at >0.05. Charts were created using GraphPad Prism version 5.01 for Windows (GraphPad Software Inc., San Diego, CA, USA; www.graphpad.com).

Results

Clinical characteristics

A total of 18 pediatric patients were included in this study. Gender distribution was as follows: nine boys and nine girls. All had been diagnosed with DS according to the diagnosis criteria established in the methodology section. The youngest patient was 4 years old, while the oldest patient was 15 years old and the median age of the participating patients was 10 years [interquartile range (IQR), 6.00–13.25 years]. The youngest age at which PER was initiated was at 1 year old for two patients. Moreover, three patients were started on PER at 13 years old, the latest among the study participants. The median age of PER initiation was 8 years (IQR, 4.75–10.75 years). Further individualized details on the patients, including their weight and seizure onset, are presented in *Table 1*. Most of the patients had two types of seizures (61.1%), followed by three types (22.2%). Among different seizure types, GTCS was the most frequently reported form and manifested in all participating patients. The youngest age of seizure onset was 4 months, while the oldest was at 3 years old. Surgical procedures were performed on six patients; and only one had diet modification (ketogenic diet). Patients' characteristics are displayed in *Table 2*. Regarding the patients' genetic background, whole exome sequencing (WES) testing revealed a mutation in the *SCN1A* gene in 94.4% with the remaining having a mutation in the *PCDH19* gene. Heterozygosity was confirmed among the majority of the mutation carriers (61.1%). Detailed data on the pathogenic variant were presented in *Table 3*.

PER efficacy and concomitant ASMs

The mean efficacy of PER was 29.17%±29.368%, with only one patient with 100% efficacy to PER. The mean maximum dose of PER in milligrams per day (mg/day) was 6.67±1.680 mg. The used doses ranged from 4 to 8 mg. The mean duration in which the patients took PER in weeks was 37.22±48.35, with a patient (case No. 13) being the only one exceeding more than 52 weeks on PER (208 weeks) (*Table 4*). Five patients were currently on two or fewer ASMs. A single patient had the highest number of concomitant ASMs with a total of five medications, including lamotrigine, topiramate, clobazam, valproic acid, and stiripentol. The most commonly used concomitant ASM was valproic acid and clobazam (n=12) (*Figure 2*). Our patients took different ASMs in the past, but many of them failed to manage their symptoms. Six patients had two or fewer failed ASMs, while others had more than two failed medications. PER was the most frequently reported medication among the past failed ASMs (n=14).

Adverse effects of PER

Among the patients, seven patients reported side effects after the administration of PER. These adverse effects included sleepiness (n=3) and drowsiness (n=5). The severity of those

Table 1 Demographics and characteristics of patients treated with PER

Case No.	Age (years)/sex	Weight (kg)	Age of seizure onset	Age at initiation of PER	Seizure types at PER introduction
1	10/F	28	3 years	8 years	Focal febrile seizure, GTCS, recurrent status epilepticus
2	13/M	15	6 months	9 years	Focal febrile seizure, GTCS
3	14/F	77	6 months	1 year	Focal febrile seizure, GTCS
4	6/F	19	10 months	5 years	Focal febrile seizure, GTCS
5	12/M	23	1 year	10 years	Focal febrile seizure, GTCS, myoclonic seizure
6	6/M	23	4 months	5 years	Focal febrile seizure, GTCS
7	10/F	39	8 months	9 years	Focal febrile seizure, GTCS
8	9/M	25	6 months	7 years	Complex febrile partial seizure, GTCS, myoclonic seizure, head drops
9	11/M	13	4 months	9 years	GTCS, tonic seizure
10	10/F	28	1 year	2 years	Focal febrile seizure, GTCS
11	4/M	13	4 months	3 years	Focal febrile seizure, GTCS, myoclonic seizure
12	15/M	47	1 year	13 years	Focal seizure, GTCS
13	5/M	18	6 months	1 year	Drop attack, GTCS, myoclonic seizure
14	5/F	17	6 months	4 years	GTCS
15	8/F	25	1 year	6 years	Focal febrile seizure, GTCS
16	15/F	37	1 year	13 years	GTCS
17	15/F	57	1 year	13 years	Focal seizure, GTCS
18	11/M	27	6 months	8 years	Focal febrile seizure, GTCS

M, male; F, female; PER, perampanel; GTCS, generalized tonic-clonic seizure.

Table 2 Patients' characteristics, demographics, and PER use details

Variables	Mean	SD	Median	IQR
Age (years)	9.94	3.670	10.00	6.00–13.25
Age at initiation of PER (years)	7.67	3.865	8.00	4.75–10.75
Maximum dose of PER taken (mg)	6.67	1.680	8.00	5.50–8.00
% of drug efficacy	29.17	29.368	25.00	0.00–50.00

PER, perampanel; SD, standard deviation; IQR, interquartile range.

adverse effects were variables as demonstrated in *Table 4*. A single patient reported a severe form of drowsiness. Other patients reported no adverse effects after the administration of PER. Detailed data on each patient were presented in *Table 4*.

Bivariate analysis

When assessing the factors affecting the efficacy of PER, patient age had an inverse correlation, as patients younger in age had a higher efficacy rate (r=−0.383, P=0.11). Furthermore, when dividing the patients into two groups (≤8 years old; 6 patients, and >8 years old; 12 patients), the first group had a significantly higher efficacy rate when using PER than the second (49.17%±34.120% *vs.* 19.17%±21.829%, P=0.03). There was a positive correlation between the max dose and the efficacy of PER, but it was not significant (r=0.358, P=0.14). However, the only patient with 100% efficacy was one with the maximum drug dose (8 mg). The

Table 3 Summary of patients' genetic mutation and zygosity in relationship to seizure age of onset

Case No.	Gender	Age of onset	Pathogenic genetic mutation	Zygosity
1	Female	3 years	SCN1A: NM001165963:exon16:c.3135delA:p.L1045fs	Heterozygous
2	Male	6 months	SCN1A: C.680T>G p.Ile227Ser Chr2 166909376 Exon 5	N/A
3	Female	6 months	SCN1A: NM_001165963.2:exon3–8:chr2:166903258-166913051del9793bp	Heterozygous
4	Female	10 months	SCN1A	N/A
5	Male	1 year	SCN1A: NM_001165963:exon16:c.2985T>G:p.F995L	Heterozygous
6	Male	4 months	SCN1A: NM_001165963:exon24:c.4497delT:p.F1499fs	Heterozygous
7	Female	8 months	SCN1A: NM_001165963:exon16:c.3225T>A:p.Y1075X	Heterozygous
8	Male	6 months	SCN1A: NM_0011659631:exon :c.3867_3869del:p.F1289del chr2:166868628	Heterozygous
9	Male	4 months	SCN1A	N/A
10	Female	1 years	SCN1A	N/A
11	Male	4 months	SCN1A: NM_001165963.4:exon14:c.1852C>T:p.Arg618Cys	Heterozygous
12	Male	1 year	SCN1A: NM_001165963.4:exon11:c.1177C>T:p.Arg393Cys	Heterozygous
13	Male	6 months	SCN1A	N/A
14	Female	6 months	SCN1A: NM_001165963:exon16:c.3091T>C:p.Y1031H	Heterozygous
15	Female	1 year	SCN1A: NM_001165963:exon26:c.5010_5013del:p.L1670fs	Heterozygous
16	Female	1 year	SCN1A	N/A
17	Female	1 year	PCDH19: NM_001184880.1:exon1:c.464A>G:p.Asp155Gly	N/A
18	Male	6 months	SCN1A: NM_0011659631:exon :c.5010_5013del:p.F1671Tfs	Heterozygous

N/A, not available.

Table 4 Response to PER (efficacy, adverse effects, and maximum dose) and the use of concurrent and past ASMs

Case No.	Age at initiation of PER (years)	Maximum dose of PER (mg)	Adverse effects of PER	Current ASMs used by the patient	Number of past failed ASMs used by the patient	Non-pharmacological intervention	PER efficacy (%)
1	8	4	Sleepiness	Lamotrigine, topiramate, clobazam, valproic acid, stiripentol	Lacosamide, perampanel	No	0
2	9	6	Sleepiness	Valproic acid, zonisamide	Topiramate, levetiracetam, steroid, clonazepam, clobazam, rufinamide, lamotrigine, cannabinoid, perampanel	No	50
3	1	8	None	Levetiracetam, perampanel, clobazam, valproic acid	Topiramate, carbamazepine, lamotrigine, rufinamide	No	50
4	5	4	None	Valproic acid, phenobarbitone, clobazam	Perampanel, levetiracetam, topiramate	Surgery: vagal nerve stimulation	0

Table 4 *(continued)*

Table 4 *(continued)*

Case No.	Age at initiation of PER (years)	Maximum dose of PER (mg)	Adverse effects of PER	Current ASMs used by the patient	Number of past failed ASMs used by the patient	Non-pharmacological intervention	PER efficacy (%)
5	10	6	Drowsiness	Levetiracetam, valproic acid, topiramate	lamotrigine, perampanel	No	0
6	5	8	None	Perampanel, clobazam, levetiracetam, topiramate	Valproic acid	No	100
7	9	6	None	Valproic acid, clobazam	Perampanel, levetiracetam, Topiramate, lamotrigine, carbamazepine, phenobarbitone, clonazepam	No	0
8	7	4	Drowsiness Sleepiness	Clobazam, stiripentol	Perampanel, topiramate, carbamazepine, clonazepam, oxcarbazepine, valproic acid, levetiracetam, lamotrigine, ethosuximide, cannabinoid	Surgery: vagal nerve stimulation + corpus callosotomy	0
9	9	6	Drowsiness	Lacosamide	Perampanel, levetiracetam, valproic acid, clonazepam, clobazam, phenobarbitone	No	30
10	2	8	None	Levetiracetam, clobazam, topiramate	Valproic acid, carbamazepine, lamotrigine, phenobarbitone, perampanel	No	50
11	3	8	None	Perampanel, levetiracetam, valproic acid, lamotrigine	Lacosamide, phenobarbitone, topiramate, carbamazepine, prednisone, clonazepam	Diet modification: keto diet	60
12	13	8	None	Lacosamide, lamotrigine, clobazam	Perampanel, levetiracetam	Surgery: focal epilepsy surgery (focal cortical dysplasia)	0
13	1	8	None	Perampanel, valproic acid, phenobarbitone	Levetiracetam, clonazepam, Carbamazepine, topiramate	No	50
14	4	4	Severe drowsiness	Clobazam	Perampanel, valproic acid, phenytoin, topiramate	No	60
15	6	8	None	Clobazam, levetiracetam, valproic acid	Perampanel, topiramate	No	25
16	13	8	Drowsiness	Clobazam, levetiracetam, valproic acid	Perampanel, topiramate, lamotrigine	Surgery: vagal nerve stimulation	25
17	13	8	None	Topiramate, valproic acid, levetiracetam	Perampanel, carbamazepine	Surgery: temporal lobectomy (gliosis)	25
18	8	8	None	Clobazam, valproic acid, stiripentol	Perampanel, topiramate, levetiracetam, clonazepam, lamotrigine	Surgery: temporal lobectomy (gliosis): vagal nerve stimulation	0

PER, perampanel; ASM, anti-seizure medication.

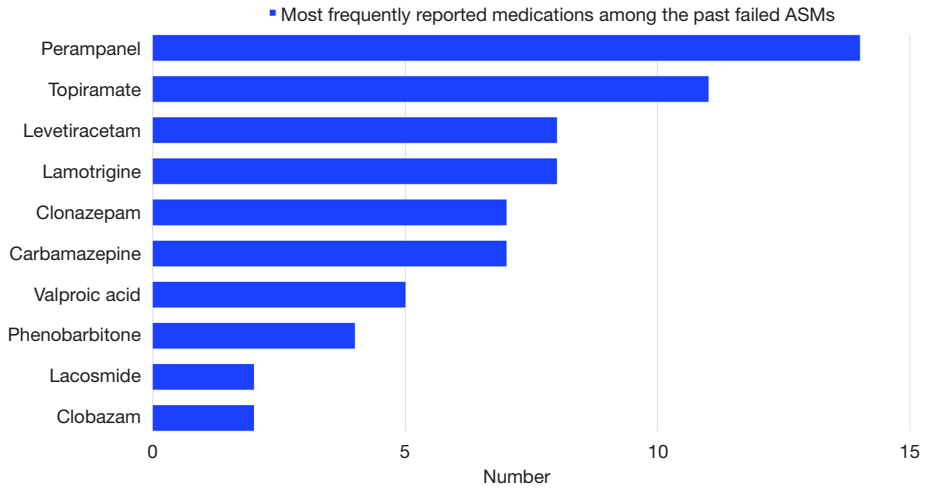

Figure 2 Most frequently reported medications among the currently used ASMs. ASMs, anti-seizure medications.

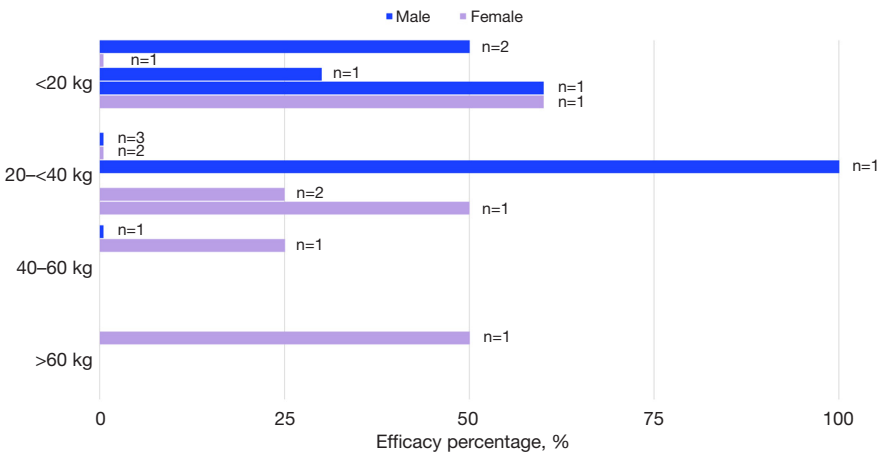

Figure 3 Efficacy rate at different perampanel doses across participants' weight. X-axis represents the efficacy in percentage. Y-axis represents the patient weight. n, number of patients.

number of drug side effects was positively correlated with the drug efficacy. However, the relationship was not significant (r=–0.235, P=0.34). Nevertheless, the only patient with more than one side effect had an efficacy rate of 0% (*Figure 3*).

Discussion

In this study, we investigated the efficacy and tolerability of PER in patients with DS. Despite its rare prevalence, it manifests with interactable epilepsy that requires timely intervention and an accurate diagnosis (3). Next-generation sequencing (NGS), especially WES testing, aids personalized management strategies for patients and families. These advances in NGS are key in diagnosing and guiding treatment in current clinical practice (31). In the case of patients with DS, early and accurate diagnosis can lead to withholding specific ASMs that proven less effectivity among those patients, namely, carbamazepine, lamotrigine, phenytoin due to their inhibitory role on sodium channels (32). However, there are several more effective substitutes that includes levetiracetam, valproic acid, topiramate, clobazam, zonisamide, and stiripentol (33). However, some DS patients still have interactable seizures, and the causes remain unknown for some. Medication availability can also be an issue, with certain countries having limitations on drugs like clobazam and stiripentol. Previous

Table 5 Efficacy of PER in different literature findings

Author	Study design	Patient response	Study date
Current study	Observational, retrospective	7 pediatric patients with PER efficacy of >50%	2023
Nissenkorn *et al.* (24)	Observational, retrospective	11 patients with PER efficacy of >50% (6 patients had >90% reduction in seizure)	2023
Chang *et al.* (29)	Observational, retrospective	2 pediatric patients with PER efficacy of >50%	2020
Yoshitomi *et al.* (30)	Observational, retrospective	5 pediatric patients with PER efficacy of >50%	2019
Lin *et al.* (28)	Observational, retrospective	4 pediatric patients with PER efficacy of >50% (2 patients had >90% reduction in seizure)	2018
Swiderska *et al.* (27)	Prospective and retrospective	The study enrolled 1 pediatric patient with early discontinuation due to lack of seizure control	2017
De Liso *et al.* (26)	Observational, retrospective	1 patient with PER efficacy of >50%	2016
Biró *et al.* (25)	Observational, retrospective	1 patient with PER efficacy of >50%	2015

PER, perampanel.

studies found that around 80% of patients with DS have a mutation in the *SCN1A* gene, which is a subunit gene of the voltage-gated sodium channel (4) (*Table 3*). Speculating into the molecular level, evidence has been demonstrated that most of these mutations are paternally derived due to higher rates of mitoses during spermatogenesis than oogenesis (34). The mean age of our patients was 9.94±3.670 years (range, 4–15 years) (*Table 2*), and the average age in the studies by Yoshitomi *et al.* [2019] and Lin *et al.* [2018] was 11.5±2.2 years (range, 7–15 years) and 14.4±2.3 years (range, 12–17 years), respectively (28,30). Although this study comes to fill the gap of prior studies and to assess the efficacy among younger populations, further studies are required among younger age groups and toddlers that frequently exhibit refractory epilepsy (35-37). Seven of our patients (38.9%) presented with an efficacy of ≥50%. In other literature, percentages of favorable seizure reduction (≥50%) were observed among 80% of DS patients (28), While other studies included a single patient with DS (26,27), and two patients (25). Collectively, the efficacy rate was estimated at 66.7% of patients with DS. Other studies with a slightly higher number of participants showed that the efficacy rate was moderately reduced (62.5%) (30). Moreover, our results found younger patients showed a significantly higher PER efficacy rate compared to older ones. There have been varying views in the literature about the correlation, as Fernandes *et al.* [2021] noted a similar trend but encouraged further studies to confirm such findings (38), while Swiderska *et al.* [2017] and Hwang *et al.* [2020] noted no significant relationship between age and efficacy (27,39). A study conducted by Rohracher *et al.* [2018] found the contrary, in which the prevalence of patients who became seizure-free was observed among higher age groups (40). A summary of other studies was presented in *Table 5*. The most common concomitant ASMs are represented in *Figure 2*. A study by Goa *et al.* [2022] showed that early add-ons (defined as previously using two or fewer ASMs) had a greater responder rate than a late add-on. However, there was no statistical significance (41). Notable side effects including irritability with aggressiveness, loss of appetite and diplopia were reported (26). In a different study, a couple of patients developed suicidal thoughts after commencing PER, where these suicidal thoughts subsequently resolved after the withdrawal of PER in the two patients (27). Furthermore, some observation suggested an action pattern of "all-or-nothing" for PER. This description for such observation was set after noticing that if PER is effective in controlling one seizure type it will be effective in the control of other types (30). This study provides new evidence supporting the effectiveness of PER in reducing multiple forms of seizure in patients with DS. However, further research is needed to understand the variation in efficacy rates and individual responses to PER. This is the largest study conducted on PER's effects in DS patients and the first in our region. It has limitations, including its retrospective design, small sample size, and limited prior literature for comparison. Efficacy reporting may also be influenced by other interventions and clinical observations, not solely PER.

Conclusions

Our study aimed to assess the efficacy of PER among

pediatric patients with DS. The results of our study revealed a significant relationship between the younger aged patients and the increase in the efficacy of PER. Moreover, other factors such as the dose given had some effect on the efficacy as well. In conclusion, this study presented evidence of promising therapeutic potentials for PER among some patients with DS, with data supporting the value of this treatment. However, additional studies are still required to confirm and verify the current findings. We recommend that a double blinded clinical trial with a control and an experimental group to be conducted in order to further support the current evidence on the use of PER to treat DS in pediatric population.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-581/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Unit of Biomedical Ethics at the Faculty of Medicine at King Abdulaziz University approved this study (reference number: 244-23) on May 2, 2023. Informed consent was obtained from the parents or legal guardians of all patients. Informed consent was also obtained for off-label use of PER on the patients.

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